PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

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09. Okt. 2003

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Applicant's or agent's file reference 3605P111WO HO/gf	Date of mailing (day/month/year) 09.10.2003
	IMPORTANT NOTIFICATION
International application No. PCT/EP02/04281	International filing date (day/month/year) 18.04.2002
	Priority date (day/month/year) 19.04.2001
Applicant NMI NATURWISSENSCHAFTLICHES UND MEDIZINISCHES...	

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Danti, B Tel. +49 89 2399-8161

PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 3605P111WO HO/gf	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP02/04281	International filing date *(day/month/year)* 18.04.2002	Priority date *(day/month/year)* 19.04.2001
International Patent Classification (IPC) or both national classification and IPC G01N33/00		
Applicant NMI NATURWISSENSCHAFTLICHES UND MEDIZINISCHES...		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand 05.10.2002	Date of completion of this report 09.10.2003
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Stricker, J-E Telephone No. +49 89 2399-8395

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP02/04281

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-18 as originally filed

Claims, Numbers

18-20 received on 16.08.2003 with letter of 14.08.2003

1-17 received on 07.10.2003 with letter of 07.10.2003

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP02/04281

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-17
	No:	Claims	none
Inventive step (IS)	Yes:	Claims	1-17
	No:	Claims	none
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	none

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET

International application No. PCT/EP02/04281

Section V

1. Reference is made to the following documents:

D1: VAN HEYNINGEN V; BROCK D J H; VAN HEYNINGEN S, "A SIMPLE METHOD FOR RANKING THE AFFINITIES OF MONO CLONAL ANTIBODIES", Journal of Immunological Methods, 1983, vol. 62, No. 2, p.147-154, ISSN 0022-1759, XP009017607.

D2: STANLEY C; LEW A M; STEWARD M W, "THE MEASUREMENT OF ANTIBODY AFFINITY A COMPARISON OF 5 TECHNIQUES UTILIZING A PANEL OF MONO CLONAL ANTI DI NITRO PHENOL ANTIBODIES AND THE EFFECT OF HIGH AFFINITY ANTIBODY ON THE MEASUREMENT OF LOW AFFINITY ANTIBODY", Journal of Immunological Methods, 1983, vol. 64, no. 1-2, p.119-132, ISSN 0022-1759, XP009017610.

These documents were not cited in the international search report.

2. The ranking of compounds, e.g. antibodies, in terms of affinity existed already in the art, cf. D1 and D2. Knowing the exact concentration is not necessary, several dilutions are sufficient (cf. D1). In D2, the method involving equilibrium dialysis is performed (cf. abstract and p.121, third paragraph).

In the known prior art dealing with ranking of antibodies by affinity, it would however appear that a second target was neither used nor rendered obvious in order to provide an alternative method to those disclosed in D1 and D2. Thus, the subject-matter of claim 1 would appear to be novel and to involve an inventive step (Art. 33(2) PCT).

Claims 2-12 are dependent on claim 1 and as such also meet the requirements of the PCT with respect to novelty and inventive step. The same applies to claims 13-17 as they relate to the use of a kit for performing the novel and inventive method.

Miscellaneous

Certain defects (form or content)

Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1 and D2 is not mentioned in the description, nor are these documents identified therein.

The description should be adapted to the set of claims.

PCT/EP02/04281

October 7, 2003

NMI Naturwissenschaftliches und Medizinisches Institut an der Universität Tübingen

3605P111WO - HO/ah

Claims

1. A method for ranking at least two compounds relative to each other with respect to their first affinity constant of binding to a first target, by using their second affinity constant of binding to a second target,

wherein determination of said first affinity constant depends on the concentration of each of said compounds, and said first affinity constant depends on the composition of the respective compound, and

wherein determination of said second affinity constant depends on said concentration as well, but said second affinity constant does not depend on the composition of the respective compound,

for each compound comprising the steps of:

a) measuring a first value for said first affinity constant under equilibrium conditions; and

b) simultaneously measuring a second value for said second affinity constant under said equilibrium conditions;

and determining said first affinity constant for each compound relative to the other compound(s) by using said first and second values.

2. The method of claim 1, wherein said first target is an antigen, and wherein said at least two compounds comprise the variable domains of different antibodies binding to said antigen.

3. The method of claim 1 or claim 2, wherein said second target is an antibody or functional fragment thereof with specificity for an antibody-binding site comprised in each of said at least two compounds.

4. The method according to any one of claims 1 to 3, wherein said steps (a) and (b) are performed in parallel for multiple compounds, and wherein each compound is contained in one well or an otherwise defined area of a substrate.

5. The method according to any one of claims 1 to 4, wherein said steps (a) and (b) are performed in parallel for multiple compounds, and wherein each compound is contained in one spot of a microarray.

6. The method of any one of claims 1 to 5, wherein each of said at least two compounds is in solution.

7. The method of claim 6, wherein said steps (a) and (b) are being performed by simultaneously contacting said solution with said first and said second target, each target being immobilized on a solid phase, and wherein the amounts of compound binding to said first and second target are measured for each compound.

8. The method of any one of claims 1 to 5, wherein each of said at least two compounds is immobilized to the surface of a solid phase.

9. The method of claim 8, wherein said steps (a) and (b) are being performed by simultaneously contacting said immobilized compound with known amounts of said first and said second target in solution, and wherein the relative amounts of first and second target binding to said immobilized compound are measured.

10. The method of claim 7, wherein said first and said second target are being immobilized to different subsets of microspheres.

11. The method of claim 10, wherein said different subsets are characterized by different fluorescence labels.

12. The method of claim 11, further comprising the step of identifying binding of a compound to said first or second subset of microspheres by binding of a fluorescence label to the compound.

13. Use of a kit for performing the method of anyone of claims 1 to 12, said kit comprising

a) a first carrier comprising a least two areas for retaining sample solutions;

b) a second carrier comprising, for each of said areas comprised in said first carrier, at least two posi-

tions suitable for the immobilization of at least a first and a second compound, wherein said second carrier and said first carrier can be brought in contact in a way which allows to simultaneously contact each of said solutions with at least said first and second compounds immobilized to said at least two positions, and wherein the amounts of material out of said sample solution binding to said first and second compounds can be measured for each said sample solution.

14. Use of a kit for performing the method of anyone of claims 1 to 12, said kit comprising

a) a first carrier comprising a least two areas for retaining sample solutions;

b) a second carrier comprising, for each of said areas comprised in said first carrier, at least two positions suitable for the immobilization of at least a first and a second target, wherein said second carrier and said first carrier can be brought in contact in a way which allows to simultaneously contact each of said solutions with at least said first and second target immobilized to said at least two positions, and wherein the amounts of material out of said sample solution binding to said first and second targets can be measured for each said sample solution.

15. Use of a kit for performing the method of anyone of claims 1 to 12, said kit comprising a set of at least two different subsets of microspheres, the microspheres in each of

said subsets thereof having immobilized thereon a target for compounds to be ranked with respect to the first physicochemical property, the targets in different subsets being different, and preferably a set of at least two compounds, each being able to bind to a respective one of the at least two targets.

16. Use of a kit for performing the method of anyone of claims 1 to 12, said kit for ranking antibodies with respect to their affinity to a target, comprising a set of at least two different subsets of microspheres, the microspheres in a first subset having immobilized thereon a capture molecule for antibodies, the microspheres in a second subset being pre-activated so that the target can be immobilized thereon.

17. The use of claim 16, said kit further comprising a detection antibody.